

S/N 09/182,645



PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Jia-He Li and Jie Zhang	Examiner:	Wang, Shengjun
Serial No.:	09/182,645	Group Art Unit:	1617
Filed:	October 30, 1998	Docket No.:	70003.0001US01
Title:	Pharmaceutical Compositions Containing Poly(ADP-Ribose) Glycohydrolase Inhibitors and Methods of Using Same		

APPELLANTS' REPLY BRIEF

BOX AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner,

Pending method claims 46-49 are not anticipated, either inherently or expressly by the cited references, as the cited references do not contain all of the elements of the claims. The references are silent as to therapeutic treatment of cardiac or neural tissue damage. In addition, there are no PARG inhibitors present, either expressly or inherently. The assertion that lignin glycoside, a known PARG inhibitor, is found in the cited Wang and Ning references is unfounded and should be rejected.

The claims are also enabled by the teachings of the present specification. The specification discloses dozens of known PARG inhibitors and amply demonstrates how one of skill in the art would identify additional PARG inhibitors. The Examiner's insistence on having a defined structure for each and every PARG inhibitor never was and still is not the legal standard for determining enablement of method claims.

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BOARD OF PATENT APPEALS
AND INTERFERENCES

I. **Claims 46-49 are not Anticipated**

The rejection of claims 46-49 as being inherently anticipated under 35 U.S.C. § 102(b) by Wang and Ning¹ is unsupported and ignores the actual disclosure of each reference.

As they relate to the present claims 46-49, the cited references do not disclose, expressly or inherently, each and every element of the present claims and are deficient in at least two respects: they do not teach the therapeutic goals of the claimed invention; and they do not teach that a PARG inhibitor can achieve the claimed therapeutic goals.

A. **Wang and Ning do not Teach Treatment of Cardiac and Neural Tissue Damage**

The Examiner contends that Wang teaches the use of ginseng tea to treat and prevent diabetes. See Examiner's Answer at 5. However, apart from the ginseng tea being sugar-free, Wang does not provide any evidence that ginseng tea will result in the treatment of diabetes. Nonetheless and regardless of whether Wang teaches "treatment or prevention" of diabetes, Wang simply does not teach treatment of neural or cardiac tissue damage as required by the present claims. Diabetes is not cardiac or neural tissue damage. As such, Wang does not anticipate the present claims, even if a PARG inhibiting lignin glycoside would be present in the tea (which Tanuma teaches it is not).

The Examiner asserts that Ning teaches treatment of ischemia with ginseng tea. See Examiner's Answer at 6. Ning extols a wide range of unsupported health benefits of coffee ginseng flavored tea, specifically stating, "It can be used as a concentrate or beverage, combining medicine, health protecting effects and beverage in one and suitably applicable to middle-aged and elderly individuals experiencing prostration due to a long illness, neurasthenia, myocardial ischemia and cerebral physical exhaustion." (Ning, Ex. B, p 1, Abstract). Regardless of whether

¹ Tanuma has been used to supply missing descriptive matter. See Examiner's Answer at 8, stating, that Tanuma teaches that "ginseng hot water extract containing [sic] the lignin glycoside herein . . . Therefore the claimed method herein read [sic] on the method taught by Wang and Ning."

the teachings of Ning are supported, a teaching of providing health-protecting effects to people experiencing prostration due to myocardial ischemia is not a teaching of treating cardiac tissue damage. Thus, Ning does not anticipate the present claims, even if one were to assume that a PARG inhibiting lignin glycoside would be present in the tea.

Tanuma does not teach treatment of cardiac or neural tissue damage, and the Examiner has never so asserted. Thus, Tanuma alone does not anticipate claims 46-49.

B. Tanuma does not Teach that a PARG Inhibiting Lignin Glycoside
Must Necessarily be Present in the Ginseng Teas of Wang and Ning

Regardless of whether Wang and Ning teach the therapeutic goals of the claims 46-49, the Examiner has failed to meet the burden of establishing that the ginseng teas of Wang and Ning contain a PARG inhibiting lignin glycoside. To show inherency, the Examiner must provide a basis in fact or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. See Ex parte Levy, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Inter. 1990); see also MPEP § 2112.

In attempting to establish that the ginseng teas of Wang and Ning contain a lignin glycoside, the Examiner stated (without citation to reference) that because lignin is commonly found in plant materials (see Examiner's Answer at 5), the ginseng teas of Wang and Ning must contain an PARG inhibiting lignin glycoside (see generally Examiner's Answer at 5-8). More specifically, the Examiner stated, "Tanuma teach [sic] that ginseng hot water extract containing [sic] the lignin glycoside herein . . . Therefore the claimed method herein read [sic] on the method taught by Wang and Ning" (Examiner's Answer at 8). However, the teachings of Tanuma suggest that the teas of Wang and Ning would not contain a lignin glycoside.

Tanuma teaches one skilled in the art that a lignin glycoside is not to be found in a hot water extract of a crude vegetative product (such as a pine cone, ginseng, etc.) as suggested by the Examiner. The extraction method presented in Tanuma places a pine cone in water as the first step in the extraction procedure. The lignin glycoside remains in the pine cone during this step and does not get extracted in the water. (See Tanuma, Ex. C, at Embodiment 1, pp. 6-7).

The method of extraction taught by Tanuma is summarized below:

- (1) boil pine cone in water for 2 hours three times (lignin glycoside still in pine cone);
- (2) half dry pine cone and immerse in ethanol overnight (lignin glycoside still in pine cone);
- (3) half dry pine cone and immerse in acetone overnight (lignin glycoside still in pine cone);
- (4) dry pine cone and extract in 1N NaOH for 6 hr (or overnight), add acetic acid to pH = 5.0 then remove precipitate by high speed centrifugation (lignin glycoside is now in solution);
- (6) add ethanol to extracted solution (containing lignin glycoside) and let stand overnight on cold room;
- (7) remove precipitate by high speed centrifugation, dialyze supernatant (containing lignin glycoside) in water;
- (8) freeze dry dialyzed solution and obtain powder (containing lignin glycoside); and
- (9) refine powder by gel filtration to begin to obtain a purified and useful lignin glycoside. (See Tanuma, Ex. C, at Embodiment 1, pp. 6-7).

As can be seen from a close inspection of the extraction process, Tanuma does not teach that a lignin glycoside can be extracted from a crude vegetative product (*i.e.*, pine cones, ginseng root, etc.) in hot water—it's not soluble in boiling water, even after six hours. Accordingly, whatever lignin glycoside is present in the ginseng root of Wang and Ning would remain in the root and not transfer to the tea that is consumed by an individual. Thus there is no therapeutic action by lignin glycoside or any PARG inhibitor in Wang and Ning.

The Examiner has also failed to provide any evidence that the lignin glycoside would be present in an amount effective to treat cardiac or neural tissue damage. The Examiner's mere assertion that:

In view of the fact that ginseng is a valid source of lignin glycoside the dosage form of Wang or Ning would have reasonably expected to contain such [therapeutic] amount[s] of lignin glycoside (Examiner's Answer at 7),

is insufficient to meet the burden of showing that the teas of Wang and Ning necessarily contain therapeutic amounts of a lignin glycoside and ignores the teaching of the references cited by the Examiner. Even assuming that a small amount of lignin glycoside were to be present in the aqueous phase of the first step of Tanuma (boiling for 2 hours, three times), there is simply no evidence that placing ginseng root in mere hot water to make tea as taught by Wang and Ning would result in active lignin glycoside in an amount effective to inhibit PARG.

In sum, the references cited by the Examiner do not teach a PARG inhibitor as useful for treatment of cardiac or neural tissue damage as required by the present claims 46-49. The present claims are not anticipated by cited references. Applicants respectfully request that the Board reverse the anticipation rejection of claims 46-49.

II. **The Claims are Patentable over Wang or Ning,
in View of Tanuma AB or AC, and in Further View of Kim and Wen**

Wang, Ning, and Tanuma, alone or in combination do not teach that a PARG inhibitor can be useful for treatment of cardiac or neural tissue damage. The health benefits, if any, of ginseng tea taught by Wang and Tanuma cannot be due to lignin glycoside, a PARG inhibitor, because Tanuma suggests the lignin glycoside from a crude vegetative product (*i.e.*, a pine cone, ginseng root, etc.) cannot be extracted in hot water. Kim and Wen do not overcome the deficiencies of Wang, Ning, and Tanuma.

According to the Examiner, Kim and Wen teach that ginseng is useful for treatment of ischemia and reperfusion injury. (See Examiner's Answer at 9). However, neither Kim nor Wen teach that a PARG inhibitor can be useful for treatment of ischemia or reperfusion injury. Kim, like Wang and Ning, teaches whole ginseng and adds nothing. Wen, however, would actually lead one of skill in the art away from the currently claimed invention, as Wen teaches that compounds other than PARG inhibitors may be responsible for the disclosed effects. (See Appellants' Supplemental Brief at 6 for further discussion).

There is nothing in any of the cited references, alone or in combination that would suggest to one of skill in the art that PARG inhibitors would be useful for treatment of cardiac or neural tissue damage. Claims 46-49 are not obvious over the cited references. Applicants respectfully request that the Board reverse the obviousness rejection of claims 46-49.

III. **Claims 46-49 to PARG Inhibitors are Enabled**

A. **Claims 46-49 satisfy the Wands factors**

"The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 279 (1916) which postured the question: is the experimentation needed to practice the

invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988)." MPEP § 2164.01

"The test for what constitutes undue experimentation is not merely quantative, since a considerable amount of experimentation is permissible, if it is merely routine. . ." *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. *See also* MPEP § 2164.06. Further, a patent need not disclose what is well known in the art. *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). See also MPEP § 2164.01.

As the Examiner indicated but did not address in detail, the Federal Circuit in *In re Wands* set forth eight factors for considering whether a specification is enabling. Applying the Wands factors to the facts presently at issue results in the conclusion that nothing more than permissible routine testing as would be understood by one skilled in the art would be required to practice the invention as claimed in claims 46-49.

1. The quantity of experimentation necessary

As mere routine experimentation is required to practice the claimed invention commensurate with the scope of claims 46-49, the quantity of experimentation is not undue. Such a conclusion is required by, e.g., MPEP § 2164.06: "The test for what constitutes undue experimentation is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. . ." citing *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.

The specification specifically discloses several PARG inhibitors and classes of known PARG inhibitors. For example, the specification teaches that several structurally unrelated PARG inhibitors are sufficient to produce the desired effect of claims 46-49. See, e.g., Specification, pp. 25-29 (teaching PARG inhibitors such as glucose derivatives, lignin

glycosides, hydrolysable tannins including gallotannins and ellagitannins, adenoside derivatives, acridine derivatives including 6,9-diamino-2-ethoxyacridine lactate monohydrate, tilorone analogs including tilorone R10.556, daunomycin or daunorubin hydrochloride, ellipticine, proflavine, etc.). Due to this disclosure, one of skill in the art would not have to identify a novel PARG inhibitor to practice the claimed invention. One would simply have to select from the disclosed inhibitors. Surely, this cannot be considered undue. Furthermore, one could use the disclosed compounds or classes of compounds as a starting point for routine derivation to identify additional PARG inhibitors useful for the claimed methods. One of skill in the art could run the new compounds through a routine PARG enzymatic assay to determine whether the compounds have desired PARG inhibiting activity.

The present specification describes at Example 35 such a routine PARG enzymatic assay useful for quantifying PARG activities and determining inhibition constants. (See Specification, Example 35, pp. 101-105; see also pp. 57-78). With the standard usage of high throughput screening, which companies routinely employ, one could readily screen even millions of such derivative compounds. In addition, one could test compounds structurally unrelated to those mentioned in the specification through such assays to determine whether they contain desired PARG inhibiting activity. While the quantity of such experimentation may appear great, it is nothing more than routine and thus permissible under 35 U.S.C. § 112, first paragraph.

Applicants assert that none of the above experimentation and techniques are complex. However, to the extent that they are determined to be complex, such a determination cannot result in a finding that such experimentation is undue because one of skill in the art typically engages in such experimentation:

"The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub. nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404."

MPEP § 2164.01

2. The amount of direction or guidance provided

As stated above, the specification provides adequate guidance as to what structural features a compound may need to be an effective PARG inhibitor and for those PARG inhibiting compounds of different structure, the specification provides an assay for determining whether the compound inhibits PARG. Thus the specification provides ample guidance for identification of compounds having desired activity.

In addition, the references cited in the background of the specification alone provide numerous references² discussing the structure and activity of PARG inhibiting compounds. These references also discuss additional assays useful for determining whether a compound inhibits PARG activity. As PARG inhibitors and methods for identifying compounds having PARG inhibiting activity are well known in the art, the specification need not disclose all the details of such information to be enabling. "A patent need not teach, and preferably omits, what is well known in the art." MPEP § 2164.01, citing *In re Buchner*, 929 F.2d 660,661, 18 USPQ2d. 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 91, 94 (Fed. Cir. 1986), *cert. denied*, 480 US 947 (1987); and *Lindemann*

² For example, a single paragraph at page 21 of the Specification cites the following patent documents and articles as discussing methods and compounds for inhibiting PARG: Tanuma et al., JP 042-75223-A2; Tanuma et al., JP 042-75296-A2; Tanuma, JP 032-05402-A2; Tanuma et al., JP 04-013684-A2; Slama et al., J. Med. Chem. 38: 389-393 (1995); Slama et al., J. Med. Chem. 38: 4332-4336 (1995); Maruta et al., Biochemistry 30:5901-5912 (1991); Aoki et al., Biochim. Biophys. Acta 1158:251-256 (1993); Aoki et al., Biochem. Biophys. Res. Comm. 210:329-337 (1995); Tsai et al., Biochemistry Intl. 24:889-897 (1991); and Concha et al., Biochemistry Intl. 24:889-897 (1991).

Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). See also MPEP § 2164.01.

In light of the specification and the state of the art, the specification provides adequate guidance to one of skill in the art as to how to practice the invention commensurate in scope with claims 46-49.

3. The presence or absence of working examples

While neither 35 U.S.C. § 112, first paragraph, nor any of the other sections of the Patent Statute or Patent Rules require that a specific working example be disclosed, Applicants have provided working examples directly on point as to the issue that the Examiner claims is lacking or insufficient. The specification discloses how to synthesize several exemplary PARG inhibitors (see Specification, Examples 1-6, at 50-57). The specification also shows the effectiveness of several compounds to inhibit PARG activity (*see* Specification, Test example 1, p. 57, stating that all tested compounds inhibited PARG). While no such showing is required, Applicants have exceeded the requirements of 35 U.S.C. 112, first paragraph in this respect.

4. The nature of the invention

The nature of the claimed invention involves the use of PARG inhibitors in the treatment of cardiac and/or neural tissue damage. The Examiner has never contended that the specification is insufficient for the purposes of enabling one of skill in the art, in light of the state of the art, to administer a known PARG inhibitor for such purposes. The heart of the invention of claims 46-49 lies in the discovery that PARG inhibitors can be useful in the treatment of cardiac and/or neural tissue damage.

The Examiner has made the issue to be one of the potential structures of PARG inhibitors. The discovery that PARG inhibitors are useful in treatment of cardiac or neural tissue

damage is of such a nature that it should be applicable to the use of any PARG inhibitor for such purposes. This is emphasized in the specification by the disclosure of structurally diverse PARG inhibitors, which may be used in accordance with the methods of the invention., See, e.g., Specification, pp. 25-29 (teaching PARG inhibitors such as glucose derivatives, lignin glycosides, hydrolysable tannins including gallotannins and ellagitannins, adenoside derivatives, acridine derivatives including 6,9-diamino-2-ethoxyacridine lactate monohydrate, tilorone analogs including tilorone R10.556, daunomycin or daunorubin hydrochloride, ellipticine, proflavine, etc.). Whether one uses a PARG inhibitor structurally similar to those disclosed in the specification or if one uses a structurally distinct novel PARG inhibitor, the specification provides sufficient guidance for one of skill in the art as to the nature of the claimed invention; namely, how to administer a PARG inhibitor to treat neural or cardiac tissue damage.

5. The state of the prior art

PARG inhibitors, their mechanism of actions, and assays useful for identifying PARG inhibitors are well known. As discussed throughout the background section of the present specification, PARG inhibitors had been known and were well studied. The art is replete with knowledge as to how one can synthesize and identify PARG inhibitors. The specification has adequately disclosed the inventive aspect of claims 46-49; namely, the administration of PARG inhibitors to treat cardiac or neural tissue damage. How one would go about identifying additional PARG inhibitors is not only described in the specification but also known in the art and well within the ability of one of skill in the art.

6. The relative skill of those in the art

The level of skill in the art regarding PARG inhibitors was high at the time the present application was filed. The present specification provides some indication of the level of

knowledge and skill in the art. In the background section of the present specification, for example, it is stated,

Methods and compounds for inhibiting PARG are disclosed in Tanuma et al., JP 042-75223-A2, . . . Tanuma et al., JP 042-75296-A2, . . . Tanuma, JP 032-05402-A2, . . . Tanuma et al., JP 04-013684-A2, . . . Slama et al., J. Med. Chem. 38: 389-393 (1995), . . . Slama et al., J. Med. Chem. 38: 4332-4336 (1995), . . . Maruta et al., Biochemistry 30:5901-5912 (1991); . . . Aoki et al., Biochim. Biophys. Acta 1158:251-256 (1993); . . . Aoki et al., Biochem. Biophys. Res. Comm. 210:329-337 (1995); . . . Tsai et al., Biochemistry Intl. 24:889-897 (1991); and Concha et al., Biochemisrty Intl. 24:889-897 (1991).

Specification at 21.

Additional references to PARG inhibitor art are also made throughout the specification.

The state of the art with regard to PARG inhibitors was quite high.

7. The predictability of the art

As indicate above, the nature of the invention of claims 46-49 is the discovery that PARG inhibitors can be useful for treatment of cardiac or neural tissue damage. One of skill in the art could readily predict that a given PARG inhibitor would be useful for such purposes based on the teachings of the present specification.

As for the identification as to what compounds may be PARG inhibitors, it has already been stated above that the present specification and prior art provide several viable options for one of skill in the art to identify such compounds through routine experimentation.

8. The breath of the claims

The specification discloses several classes of compounds and specific compounds useful for treating cardiac and neural tissue damage. The specification also provides an example of how to identify whether derivatives of these classes of compounds or whether new structurally unrelated compounds are PARG inhibitors, and the art is replete with such guidance as well. As

such, the breath of the claims is commensurate in scope with the teachings of the present application in light of the level of skill and knowledge in the art at the time of filing the application.

A fair application of the *Wands* factors to the facts of the present application should result in a finding that the scope of the present claims is enabled by the specification.

B. Lilly and GE are not Controlling

The Examiner's reliance on University of California v. Eli Lilly & Co ("Lilly"), 119 F.3d 1559 (Fed. Cir. 1997) and General Electric Co. v. Wabash Appliance Corp. ("GE"), 304 U.S. 364 (1937) is misplaced and such reliance underlies the Examiner's confusion between the requirements necessary for enablement between product or composition claims and method claims. In both *Lilly* and *GE*, the claims at issue were product or composition claims. In *Lilly*, the claims at issue were directed to recombinant DNA or recombinant microorganisms. *Lilly*, 119 F.3d. at 1563. The claims at issue in *GE* were product claims. See *GE*, 304 U.S. at 365, stating "The patent . . . contains process claims and product claims; only the later are here involved." The structure of the product or components of the composition in both of these cases was directly on the point of novelty, and the courts stated that additional structural features were required.³

The Examiner's assertion that one must provide the same level of structural information regarding a compound in a specification where the patent claims a method claims as where the patent claims a compound is unfounded and not the holding of the cited cases. For example, the Court in *GE* discusses that it may be perfectly acceptable to claim a product by its process. 304 U.S. at 374. Such claims are acceptable where no structural features of the product are known.

³ It should be noted that the court in *Lilly* was dealing with an issue of whether the written description of the first paragraph of 35 U.S.C. § 112 was satisfied rather than whether the specification was enabling.

As discussed above, the present specification adequately describes the how to make and use the steps of the presently claimed invention: that is, how one is to administer a PARG inhibitor to achieve the effect spelled out in method claims 46-49. In addition, the specification adequately describes how one can go about determining whether a compound inhibits PARG activity. The Examiner has never disputed this.

In light of case law governing enablement (*i.e.*, *Wands*) and the inapplicability of the cases cited by the Examiner (*i.e.*, *Lilly* and *GE*), Appellants respectfully assert that the Examiner has not made out a case that the present claims are not enabled by the specification.

IV. Related Appeals and Interferences

In the Examiner's Answer, the Examiner stated, "The brief does not contain a statement identifying the related appeals and interferences . . ." However, such a statement was supplied in Appellants' Brief at page 2, Section II, which states, "The assignee, the assignee's legal representative, and the appellants are unaware of any other appeals or interferences that will affect, be directly affected, or have a bearing on the Board's decision in this appeal."

V. Grouping of Claims

The Examiner's Answer (paper no. 33) at page 2 states, "The rejection of claims 46-49 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof."

Appellant's Brief at page 4 states, 1) claims 46-47 should be considered as a group, and 2) claims 48-49 should be considered as a group.

Appellants' Brief, at page 12, further states reasons for separate patentability of the claims as follows, "Claims 48-49 are directed to particular diseases or conditions that a PARG inhibitor will treat if administered to a mammal in need thereof. These claims represent a species of the more generic claims of 46-47. As such, applicants believe claims 48-49 are separately patentable from claims 46-47."

In view of the above, Appellants request that claims 46-47 be considered as a group and claims 48-49 be considered as a group.

VI. Conclusion

For the foregoing reasons, the rejections of Claims 46-49 should be reversed.

Respectfully submitted,

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